

DOCKET NO.: ISIS0002-102 (ISIS-4313)

PATENT

**In the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application.

Please amend claims 78-81, 93-102, and 106 as indicated below.

Please cancel claims 43-46, 68-77, 82, 89-92, 103-105, and 107-116 without prejudice to their presentation in another application.

Claims 1-77 (Cancelled).

**Claim 78 (Currently Amended)** A double-stranded RNA ~~enzyme~~ substrate comprising a duplex of a first oligonucleotide and a second oligonucleotide, wherein said first and said second oligonucleotides are not covalently linked, wherein each of said first and second oligonucleotides have a central portion having at least four consecutive ribofuranosyl residues having phosphodiester linkages, wherein said central portions are base-paired with each other in said duplex; at least one of said first and said second oligonucleotides having portions flanking said central portions having chemical modifications which make them resistant to single-stranded nucleases.

**Claim 79 (Currently Amended)** A double-stranded RNA ~~enzyme~~ substrate comprising a duplex of a first oligonucleotide and a second oligonucleotide, wherein said first and said second oligonucleotides are not covalently linked, wherein each of said first and second oligonucleotides have a central portion having at least four consecutive ribofuranosyl residues having phosphodiester linkages, wherein said central portions are base-paired with each other in said duplex; at least one of said first and said second oligonucleotides having portions flanking said central portions having chemical modifications which make them resistant to single-stranded nucleases and increase their affinity for the other oligonucleotide of the duplex.

**Claim 80 (Currently Amended)** The double-stranded RNA ~~enzyme~~ substrate of claim 78, wherein said chemical modifications are phosphorothioate linkages or 2'-methoxy modifications.

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**Claim 81 (Currently Amended)** An affinity matrix comprising the double-stranded RNA enzyme substrate of claim 78.

**Claims 82-92 (Cancelled).**

**Claim 93 (Currently Amended)** A double-stranded RNA enzyme substrate of claim 78, wherein one of said oligonucleotides has the nucleotide sequence of SEQ ID NO:8.

**Claim 94 (Currently Amended)** A double-stranded RNA enzyme substrate comprising a duplex of a first oligonucleotide and a second oligonucleotide wherein said first and said second oligonucleotides are not covalently linked, wherein each of said first and second oligonucleotides include a portion having at least four consecutive ribofuranosyl residues having phosphodiester linkages and wherein said portions are base-paired with each other in said duplex.

**Claim 95 (Currently Amended)** A double-stranded RNA enzyme substrate comprising a duplex of a first oligonucleotide and a second oligonucleotide wherein said first and said second oligonucleotides are not covalently linked, wherein each of said first and second oligonucleotides include a portion having at least four consecutive ribofuranosyl residues that are base-paired with each other in said duplex; and at least one of said first and said second oligonucleotides including a chemical modification that makes said oligonucleotide resistant to single-stranded nucleases.

**Claim 96 (Currently Amended)** A double-stranded RNA enzyme substrate comprising a duplex of a first oligonucleotide and a second oligonucleotide wherein said first and said second oligonucleotides are not covalently linked, wherein each of said first and second oligonucleotides include a portion that is base-paired with each other in said duplex; and at least one of said first and said second oligonucleotides having a further portion that includes a chemical modification that increases the affinity of said oligonucleotide for the other oligonucleotide.

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**Claim 97 (Currently Amended)** A double-stranded RNA ~~enzyme~~ substrate comprising a duplex of a first oligonucleotide and a second oligonucleotide wherein said first and said second oligonucleotides are not covalently linked, wherein each of said first and second oligonucleotides include a portion having at least four consecutive ribofuranosyl residues and where said portions are base paired with each other in said duplex; and at least one of said first and second oligonucleotides includes a chemical modification that makes said oligonucleotide resistant to single-stranded nucleases and that increases the affinity for said oligonucleotide for the other of said oligonucleotides.

**Claim 98 (Currently Amended)** A double-stranded RNA ~~enzyme~~ substrate comprising a duplex of a first oligonucleotide and a second oligonucleotide that are not covalently linked, wherein at least one of said first and said second oligonucleotides includes a chemical modification that makes said oligonucleotide resistant to single-stranded nucleases and that increases the affinity for said oligonucleotide for the other of said oligonucleotides.

**Claim 99 (Currently Amended)** A double-stranded RNA ~~enzyme~~ substrate comprising a duplex of a first oligonucleotide and a second oligonucleotide that are not covalently linked, wherein at least one of said first and said second oligonucleotides includes a chemical modification that makes said oligonucleotide resistant to single-stranded nucleases.

**Claim 100 (Currently Amended)** A double-stranded RNA ~~enzyme~~ substrate comprising a duplex of a first oligonucleotide and a second oligonucleotide that are not covalently linked, wherein at least one of said first and said second oligonucleotides includes a chemical modification that increases the affinity for said oligonucleotide for the other of said oligonucleotides.

**Claim 101 (Currently Amended)** A double-stranded RNA ~~enzyme~~ substrate comprising a duplex of a first oligonucleotide and a second oligonucleotide, wherein said first and said second oligonucleotides are not covalently linked, wherein each of said first and second oligonucleotides

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include a portion having at least four consecutive ribofuranosyl residues having phosphodiester linkages, wherein said portions are base-paired with each other in said duplex, and wherein one of said first and said second oligonucleotides comprises from eight to fifty nucleoside subunits.

**Claim 102 (Currently Amended)** The double-stranded RNA enzyme substrate of claim 101 wherein said one of said first and said second oligonucleotides comprises from twelve to thirty subunits.

**Claim 103-105 (Cancelled).**

**Claim 106 (Currently Amended)** A double-stranded RNA enzyme substrate comprising a duplex of a first oligonucleotide and a second oligonucleotide, wherein said first and said second oligonucleotides have a central portion having at least four consecutive ribofuranosyl residues having phosphodiester linkages, wherein said central portions are base-paired with each other in said duplex; at least one of said first and said second oligonucleotides having portions flanking said central portions, said portions having chemical modifications which make them resistant to single-stranded nucleases, and wherein one of said oligonucleotides has the nucleotide sequence of SEQ

**ID NO:8.**

**Claims 107-116 (Cancelled).**